Do patients with oral and oropharyngeal squamous cell carcinoma benefit from elective contralateral neck dissection? A long-term analysis

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Abstract: OBJECTIVES: Oral and oropharyngeal squamous cell carcinoma puts the patient at risk for bilateral neck lymph node metastasis. For this reason, routine bilateral neck dissection is preferred by some surgeons as the treatment of choice, even in N0-necks, despite the morbidity of this procedure. METHODS: Utilising data of 496 patients with squamous cell carcinoma of the head and neck region treated at the Department of Otorhinolaryngology and Head and Neck at the Medical University Hospital, Graz from 1999 to 2009, we retrospectively evaluated the effect of bilateral neck dissection on recurrence-free and overall survival rates in patients with oral and oropharyngeal cancer. RESULTS: Long-term survival of 152 patients with oral and oropharyngeal cancer did not show a statistical benefit of elective contralateral neck dissection in patients with contralateral clinically negative neck. Neither locoregional recurrence-free survival nor overall survival rates differed. CONCLUSION: We could not find a statistical benefit for operating on patients with oral and oropharyngeal squamous cell carcinoma with an elective neck dissection in contralateral clinically negative neck.

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Do patients with oral and oropharyngeal squamous cell carcinoma benefit from elective contralateral neck dissection? A long-term analysis

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Abstract

Objectives

Oral and oropharyngeal squamous cell carcinoma puts the patient at risk for bilateral neck lymph node metastasis. For this reason, routine bilateral neck dissection is preferred by some surgeons as the treatment of choice, even in N0-necks, despite the morbidity of this procedure.

Methods

Utilising data of 496 patients with squamous cell carcinoma of the head and neck region treated at the Department of Otorhinolaryngology and Head and Neck at the Medical University Hospital, Graz from 1999 to 2009, we retrospectively evaluated the effect of bilateral neck dissection on recurrence-free and overall survival rates in patients with oral and oropharyngeal cancer.

Results

Long-term survival of 152 patients with oral and oropharyngeal cancer did not show a statistical benefit of elective contralateral neck dissection in patients with contralateral clinically negative neck. Neither locoregional recurrence-free survival nor overall survival rates differed.

Conclusion

We could not find a statistical benefit for operating on patients with oral and oropharyngeal squamous cell carcinoma with an elective neck dissection in contralateral clinically negative neck.

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Introduction

In most countries, the 5-year overall survival rate for oral cavity and oropharyngeal cancer is around 50%[1]. Poor prognosis is most of the time due to neck lymph node metastasis. Oral squamous cell carcinoma (SCC) and oropharyngeal cancer have a high incidence of cervical micrometastasis contralaterally because of the rich lymphatic intercommunications across the midline[2]. Woolgar et al. demonstrated that in patients with oral cavity or oropharyngeal tumours, bilateral positive neck metastasis occurred in 6% and solely contralateral metastasis in 0.4% patients[3]. In oral cavity tumours, Kurita et al. found an incidence of contralateral lymph node metastasis in 14.7% of their patients[4]. The possibility of occult contralateral neck lymph node metastasis in the oral cavity and oropharyngeal SCC requires a challenging decision—whether the contralateral neck should be electively treated or not. This is especially so as some authors have stated that routine treatment of oral cavity and oropharyngeal tumour with bilateral neck dissection (ND) is an overtreatment, resulting in higher rates of morbidity and patient discomfort[5–7].

The study's purpose is to address the following question: among patients with oral cavity and oropharyngeal SCC, does elective bilateral ND, when compared with patients treated solely on the ipsilateral neck, reduce the frequency of recurrence and increase overall survival? The hypothesis of this study is as following: does ipsilateral ND in these patients offer a sound concept without increased recurrence rate or decreased overall survival rate? The specific aim of this study is to compare the disease-free and overall survival rates at 5 years between the patient cohorts and to identify patients suffering from contralateral lymph node recurrence.

Materials and methods

Study design: The investigators built a retrospective patient cohort study.

Study sample: The study sample was derived from a population of patients who presented to the Department of Otorhinolaryngology and Head and Neck (ORL) at the Medical University Hospital, Graz for treatment of an oral cavity or oropharyngeal SCC between 1 January, 1999 and 31 December, 2009. Subjects eligible for study inclusion had a SCC of the oral cavity or oropharynx with contralateral clinically negative neck, and these subjects had undergone operative resection of primary with or without adjacent adjuvant radiotherapy. Subjects were excluded from the study in case they had SCC at a location other than the oral cavity or oropharyngeal region, histological findings other than SCC, distant metastasis before ND, and patients not treated initially at the ORL at the Medical University Hospital, Graz. Patients undergoing a contralateral ND for contralateral clinically positive neck were also excluded.

Study variables: The study variables included age, sex, location of tumour, tumour size and grade, neck lymph node status, number of positive lymph nodes and histological factors (haemangiosis, lymphangiosis, capsule penetration, perineural invasion and conglomerate lymph nodes).

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Points of interest: The points of interest were the overall 5-year survival rate as the primary endpoint and the 5-year, locoregional recurrence-free survival rate as the secondary endpoint.

Treatment plan: A treatment plan was made which included the type and extent of unilateral or bilateral ND, post-operative adjuvant radiotherapy and type of tentative chemotherapy. If bilateral ND was performed, it was mainly because of the tumour size (>T3), if the primary tumour was close to the midline and/or positive lymph node status (>pN2a) on the ipsilateral neck. ND performed in the contralateral neck was suprahyoidal or supraomohyoidal ND in case of oral cavity carcinoma and supraomohyoidal or lateral selective ND in case of oropharyngeal carcinoma.

Radiotherapy, if applied, was 60 Gy in patients with negative resection margin and 66 Gy in patients with positive resection margin. The neck itself was radiated bilaterally with a dosage of 50 Gy. The first-choice chemotherapeutic agent was cisplatin. In case of complications such as advanced age or kidney malfunction, carboplatin was administered.

Data collection, management and analysis: Data were collected and processed by building a tumour database using Microsoft Access as the platform. Since data were documented in a standardised procedure, all data were obtainable.

Descriptive statistics (mean, frequency and range) were computed for each study variable. Bivariate analyses (χ^2, t test) were computed to measure the association between any two variables of interest. A log-rank test as well as the Kaplan–Meier method was used for survival analysis.

The study design was approved by the Institutional Ethic Committee and fulfilled the guidelines of the Declaration of Helsinki about Ethical Principles for Medical Research Involving Human Subjects.

Results

Patients: From 1999 until 2009, 496 patients were treated for SCC of the head and neck region at the ORL at the Medical University Hospital, Graz, Austria. Sixty-eight patients with histologically proven SCC of the oral cavity and 84 patients with SCC of the oropharynx with contralateral clinically negative neck were analyzed in this study. Details of patient included in this study are shown in Table 1. One hundred twenty-eight patients underwent ipsilateral ND only ('observation group') and 24 patients were treated with elective contralateral ND ('elective ND group').

Follow-up: The mean follow-up period was 58 months. Since follow-up started in 1999, some patients were followed-up for >10 years.

Group comparability: At the time of initial surgical treatment, the age of the patients in the observation and elective ND groups was 64 and 60 years, respectively. Sixty-eight and 84 patients had a primary tumour manifestation in the oral cavity and oropharyngeal region, respectively. There was no significant difference in the χ^2 test results between the two groups for all analysed variables. The distribution of the negative resection margin between the two groups was even. In the observation and elective ND groups, 59 (46.1%) and 13 (54.2%) patients, respectively, were treated with post-operative radiotherapy. In 15 patients (11.7%) of the observation group and 4 patients (16.7%) of the elective ND group, radiochemotherapy was administered (Table 2).

ND: Twenty-four patients underwent elective ND of the contralateral N0-neck. In 1 of 24 (4%) patients, occult cervical lymph node metastasis was found in the contralateral neck; this patient was a 55-year-old male with a T2 poorly differentiated SCC of the lateral pharyngeal wall.

There was no statistical difference in the χ^2 test results between the two groups with regard to resection margin, adjuvant therapy or type of ND (Table 2).

Recurrence-free survival: The 5-year, recurrence-free survival rate for the observation and elective ND groups was 66% and 59%, respectively, and the 5-year locoregional (lymph node) recurrence-free survival rate was 89% and 90%, respectively (Figure 1).

Overall survival: The 5-year overall survival rate was 70% in the observation arm and 72.5% in the elective ND arm (Figure 2). Despite the advanced tumour stages in our patients, 101 of 152 (66.4%) patients did not experience any recurrence during the study period.

Recurrence: Eighty-seven of 124 (70.2%) patients in the observation group and 14 of 24 (58.3%) in the elective ND group did not experience any recurrence (Table 3). In the observation group, of those 11 patients suffering lymph node recurrence, 5 patients (45.5%) did not receive adjuvant therapy and 6 patients (54.5%) received adjuvant radiotherapy. One patient with distant metastasis did not receive adjuvant therapy, 10 patients received radiotherapy and 2 received radiochemotherapy. In the elective ND group, 1 patient with lymph node recurrence did not receive adjuvant therapy, while the other patient received adjuvant radiotherapy. Both patients with distant metastasis did not receive adjuvant radiotherapy or radiochemotherapy.

One patient experienced a locoregional lymph node recurrence in the contralateral neck; this patient had a pT1 SCC of the lateral tip of the tongue, moderately differentiated with 4 ipsilateral positive lymph nodes, which were excised with a modified radical ND. Resection margins were negative; nevertheless, post-operative radiotherapy was administered. Seven months after primary treatment, recurrence was observed in the primary region, level 1–4 ipsilateral, level 2 contralateral, as well as distant metastasis. This patient had a tumour-related death 12 months after primary treatment.

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Table 1 Demographic data of 152 patients who were included in the study and separated into two groups representing two different treatment options: observation or elective contralateral ND for patients with a clinically contralateral negative neck

	Treatment of contralateral neck			
	Observation		Elective contralateral ND	
	Count	Column N (%)	Count	Column N (%)
Age	Mean = 64		Mean = 60	
Gender				
Male	100	78.1	19	79.2
Female	28	21.9	5	20.8
Localisation				
Oral cavity	56	43.8	12	50.0
Oropharynx	72	56.3	12	50.0
Classification				
PT1	42	32.8	6	25.0
PT2	48	37.5	9	37.5
PT3	21	16.4	6	25.0
PT4	17	13.3	3	12.5
Differentiation				
Well-differentiated	8	6.3	1	4.2
Moderately-differentiated	46	35.9	13	54.2
Poorly-differentiated	74	57.8	10	41.7
Lymph node status	49	38.3	14	58.3
pN0	19	14.8	0	0
pN1	56	43.8	10	41.7
pN2	4	3.1	0	0.0
pN3				
Positive lymph nodes	49	38.3	14	58.3
0	37	28.9	3	12.5
1	32	25.0	5	20.8
2–5	10	7.8	2	8.3
>5				
Perineural invasion				
No	116	90.6	24	100.0
Yes	12	9.4	0	0.0
Lymphangiosis				
No	122	95.3	24	100.0
Yes	6	4.7	0	0.0
Haemangiosis				
No	124	96.9	24	100.0
Yes	4	3.1	0	0.0
Capsule penetration				
No	106	82.8	19	79.2
Yes	22	17.2	5	20.8
Conglomerate lymph nodes[a]				
No	117	91.4	22	91.7
Yes	11	8.6	2	8.3

[a]Bulk of lymph nodes in which single lymph nodes cannot be separated histologically from each other

Discussion

The purpose of this study was to address the problem of occult contralateral neck lymph node metastases in patients with SCC of the oral cavity and oropharyngeal region. The hypothesis of this study was that bilateral ND in patients with contralateral clinically negative neck does not lead to an overall better survival or lower locoregional lymph node metastases compared to a wait-and-see procedure on the contralateral side. Specific endpoints were 5-year locoregional recurrence-free survival and 5-year overall survival; these endpoints were compared between the two different treatment options.

The results of this study confirm the hypothesis that elective treatment of contralateral clinically negative neck in patients with oral cavity or oropharyngeal SCC does not offer a higher locoregional recurrence-free survival rate or better overall survival rate. The 5-year overall survival rates were 65% and 62%, respectively ($p = 0.971$). Based on the results of this study and as known from other studies associated with higher morbidity[5–7], the benefit of bilateral ND is negligible.

Risk factors for contralateral lymph node metastasis, which are a topic of debate in the literature, include tumour size, type of invasion, tumours crossing the midline, lymphangiosis and ipsilateral lymph node status. As per the literature, tumours crossing the midline are a predictive factor for contralateral neck disease[8–10]. Ipsilateral positive lymph neck node status is expected to put the patient at a higher risk of contralateral lymph neck node metastasis[8–11]. The debate regarding the risk of tumour size and grade on contralateral neck involvement is controversial. Some authors could demonstrate the statistical significance of tumour grade[12,13] and size[9,10,13–15], but in other studies, these risk factors were found to be insignificant[16,17]. With the mode of

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Table 2 Distribution of treatment options between the observation and elective contralateral ND groups

	Treatment of clinical contralateral N0-neck			
	Observation		Elective contralateral ND	
	Count	Column N (%)	Count	Column N (%)
Resection margin				
R0	101	78.9	20	83.3
R+	27	21.1	4	16.7
Adjuvant radiotherapy				
No	55	43.0	13	54.2
Yes	73	57.0	11	45.8
Type of neck dissection				
Radical ND	17	13.3	5	20.8
Modified radical ND	40	31.3	9	37.5
Selective ND	7	5.5	1	4.2
Posterolateral ND	27	21.1	2	8.3
Supraomohyoidal ND	16	12.5	3	12.5
Expanded supraomohyoidal ND	16	12.5	3	12.5
Lateral selective ND	3	2.3	0	0.0
Suprahyoidal ND	2	1.6	1	4.2
Expanded lateral selective ND	0	0.0	0	0.0

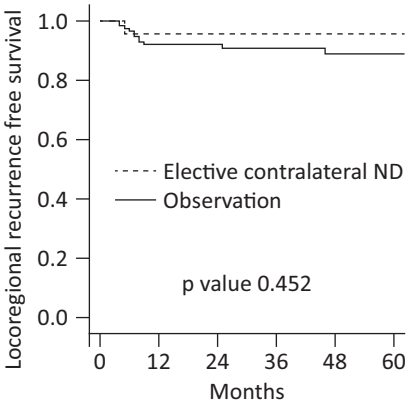

Figure 1: Locoregional recurrence-free survival considering contralateral neck treatment.

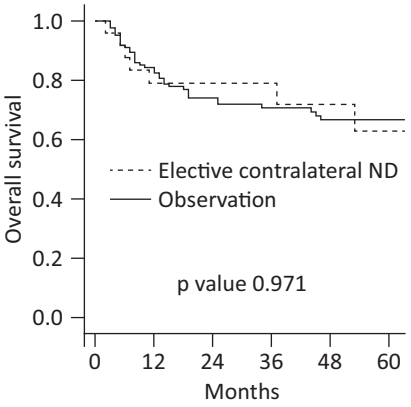

Figure 2: Overall survival considering contralateral neck treatment.

tumour invasion as a predictive factor, Goerkem et al.[13] did not observe a significant role in contralateral neck metastases, unlike in lymphangiosis. However, An et al.[12] demonstrated the importance of type and depth of tumour invasion. In our patients, contralateral ND was performed mainly due to capsule penetration, size of primary tumour, tumour crossing the midline or extensive ipsilateral neck involvement. In these situations, contralateral ND was considered but not consequently conducted.

Because of the aforementioned risk factors, discussion on the benefit of contralateral elective ND is ongoing. Further, because the guidelines and to the best of our knowledge, studies comparing the two treatment options do not exist, investigating this issue is important, especially because ultrasound diagnostic imaging and computed tomography scannings are not sensitive enough to sufficiently detect occult disease[18].

In a recent study by Fan et al. (2011), all indications for contralateral elective ND in oropharyngeal SCC were summarised as leading to: (1) tumours crossing the midline, (2) advanced staging (cT34), (3) primary tumour >3.75 mm thick, (4) multiple ipsilateral node involvement and (5) tumours arising in the base of the tongue and floor of the mouth. In case of oropharyngeal carcinoma, carcinomas of the tonsillar fossa starting with a T2 classification and carcinomas of the soft palate, base of the tongue and pharyngeal wall at any stage showed a high frequency of bilateral metastases. Therefore, all three (soft palate, base of the tongue and pharyngeal wall) carcinomas should therefore be treated with bilateral ND[19].

Interestingly, despite facing a high number of occult lymph node metastasis in the ipsilateral and contralateral neck in oral cavity and oropharyngeal cancer, the locoregional recurrence rate seems to be low. Moncrieff et al.[20] experienced an overall locoregional lymph node recurrence in 8% bilateral and 2% solely in the contralateral neck (T1 or T2 oropharyngis, any N). Considering that only 1 patient was treated bilaterally and 22 of 92 patients did not receive lymphadenectomy at all, recurrence rates of 8% bilateral and 2% solely in the contralateral neck appear to be very small.

Ten of 155 patients experienced a lymph node recurrence in a rece nt study by Sklenicka et al.[21]. This was similar to Lim et al.[22] reporting 25 of 230 patients with a recurrence in the neck. Unfortunately, the number and type of lymphadenectomy in those patients with lymph node recurrence was not described in those studies. In a retrospective study, Gonzalez-Garcia et al.[23] investigated 315 patients with oral cavity cancer, of whom,

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Table 3 Number and localisation of recurrences considering the different treatment options for the clinical contralateral N0-neck (observation vs elective contralateral ND)

Treatment of clinical contralateral N0-neck	Localisation of recurrence							
	No recurrence		Local recurrence		Lymph node recurrence		Distant metastasis	
	Count	Row N (%)	Count	Row N (%)	Count	Row N (%)	Count	Row N (%)
Observation	90	70.3	14	10.9	11	8.6	13	10.2
Elective contralateral ND	16	66.7	5	20.8	1	4.2	2	8.3

29 patients (9%) developed ipsilateral and 18 patients (5%) developed contralateral neck relapse. Further, 101 patients did not receive any lymphadenectomy, of those, 16 patients (16%) had ipsilateral relapse and only 2 patients (2%) experienced contralateral lymph node relapse.

In this study, only 1 patient experienced a contralateral lymph node recurrence. Although this patient had a very small tumour on the lateral side of the tongue, which not even close to the midline, he had one of the named risk factors (four positive lymph nodes on the ipsilateral neck). Additionally, the patient suffered from multiple recurrences (local recurrence, neck metastasis bilaterally and distant metastasis) 7 months after initial treatment.

We are aware of two potential weaknesses in this study. First, data was collected retrospectively; therefore, the number of patients is not equally distributed. Though we had majority of the patients in the observation group (n = 128) vs a much lower number in the elective contralateral ND group (n = 24), according to statistics, a valid comparison was possible. Second, patients with oral cavity and oropharyngeal carcinoma, although looked at separately, were put together for Kaplan–Meier evaluation. We looked at both tumour sites separately and same results were obtained from both groups and between both groups.

Conclusion

In this retrospective study, we examined 152 patients in two groups: those undergoing contralateral ND for N0-neck and those in which contralateral N0-necks were observed. Based on the homogeneity in these two groups, we evaluated the impact of elective contralateral ND in clinically negative necks. We could not find a significant benefit of elective contralateral ND over a wait-and-see policy in patients presenting with contralateral clinically negative neck. Even patients with high risk factors for contralateral neck lymph node metastasis can be treated without elective contralateral ND, if adjuvant therapy can be granted. The locoregional lymph node recurrence, disease-free survival and overall survival rates did not show a statistically significant difference. These results do not support the recommendation that was recently made, for example, by Olzowy et al.[19], to perform a bilateral ND in every oropharyngeal SCC, with few exceptions (T1 and selected cases of T2 of tonsillar fossa).

As per the presented data, unilateral ND is coequal regarding the 5-year overall survival and 5-year locoregional recurrence-free survival rates. Considering that unilateral ND results in less morbidity than bilateral ND is out of question.

Abbreviations list

ND, neck dissection; SCC, squamous cell carcinoma.

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